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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Diagnostic test for Parkinson's disease detection

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Diagnostic test for Parkinson's disease detection

The present invention is related to the diagnosis of Parkinson's disease and means for that purpose.

Parkinson's disease (PD) is a progressive neurodegenerative disorder, with a prevalence of 1% in the population above 65 years of age, that results in degeneration of dopamine neurons in the substantia nigra (SN), and a consequent striatal dopamine deficiency [2]. The causes and mechanism for the degeneration of dopaminergic neurons is still elusive.

There have been numerous hypotheses concerning the etiology of PD, including genetic aberrations, involvement of endogenous and exogenous derived neurotoxins and oxidative stress (OS) as a consequence of accumulation of reactive oxygen species (ROS). Many studies have been performed to identify gene mutations in PD, and some candidate genes, including superoxide dismutase and catalase, have been excluded [24]. The first gene identified as directly involved in familial form of PD is α-synuclein, coding for presynaptic protein that is defective in the disease [25,27]. Recently, a gene called Parkin, with structure similarity to the ubiquitin family of proteins, was found causing juvenile autosomal recessive form of PD [13]. Still, none of them was shown to play a common pathogenic role in idiopathic PD, since no mutations have been found in the sporadic form of the disease [26], which constitute more than 90% of the individuals affected.

A new concept in the etiology of PD is based on the study of changes in the up or down regulation of gene expression, which might increase the vulnerability of the neurons to cell death or even cause it. A number of recent studies have reported alterations in the expressions of various genes, such as a decrease in calcium-binding protein (28kDa calbindin-D) in the SN [10] and D_3 receptor mRNA in lymphocytes [20] from PD patients. Three gene alterations in the N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model for PD were observed. The first, an increase of

glutamate decarboxylase mRNA in a subpopulation of neurons in the putamen of parkinsonian monkeys, which provides further evidence that striato-pallidal GABAergic neurons are hyperactive in MPTP-treated parkinsonian monkeys [31]. The second was an increase in Bax mRNA expression (a cell death effector) in SN, with a concomitant increase in Bax immunoreactivity [9]. The third was an increase in the glutamate decarboxylase mRNA expression in a subpopulation of neurons in the putamen of Parkinsonian monkeys [31], as well as in adult rats striatum depleted of dopamine via 6-hydroxydopamine (6-OHDA), another animal model for PD, as neonates, with parallel increase in preproenkephalin and a decrease in preprodynorphin mRNA levels [15]. Furthermore, an increase in interleukine-1 beta (IL-1β) mRNA was also reported in methamphetamine treated rats [34]. As well as toxic regimen of methamphetamine caused a significant increase in the pro-death Bcl-2 family genes BAD, BAX, and BID. Concomitantly, there were significant decreases in the anti-death genes Bcl-2 and Bcl-XL [4,12]. Nonetheless, no global assessment of gene expression has been made in PD so far, that might explain the genetic events occurring in nigro-striatal dopaminergic neurodegeneration.

Current accepted clinical criteria for the diagnosis of PD, such as Unified Parkinson's Disease Rating Scale (UPDRS) [6], provide high sensitivity for detecting parkinsonism [3]. There are no sensitive and specific biochemical markers that can be used to reliably diagnose clinical and especially preclinical PD. It is now known that some PD kindreds have a mutation of the α-synuclein gene, but this cannot be used as a genetic marker for most familial and sporadic cases.

A further approach in the diagnosis of PD is functional imaging, which provides a means of discriminating typical from atypical PD, revealing characteristic patterns of loss of dopaminergic function. In addition, positron emission tomography (PET) and single photon emission tomography (SPECT) show preserved levels of striatal metabolism and dopamine receptor binding in PD, whereas levels are reduced in the atypical variants [3]. Still these tools do not give us an exact diagnosis of PD, often experts in PD changed their diagnoses infrequently during the 7.6-year follow-up [11].

More over, all these diagnostic methods are able to detect subjects with PD only after nearly 70% of the neurons have been degenerated, as only at this point symptoms appears [35]. This of course, makes treatment and may be even rescue of the neurons nearly impossible. In view of this, it is desirable to diagnose the disease at an early stage and for this reason, it is important to develop an early diagnostic method.

The problem underlying the present invitation is the fact, that no early diagnostic method in patients exists, which can be used for monitoring of PD at an early stage, before damage of neurons occurred and typical symptoms appeared [3]. It is most important to find an easy diagnostic tool for PD in biological material, as it will provide to treat before the symptoms occur. The test should be specific and sensitive and easy to perform.

There are already many drugs that show neuroprotective effects in vitro and in vivo [5,7,8,14,21,22,28,29,32]. Additionally, gene therapy was shown to be most successful in delaying the neurodegenerative process [1,16-19,23,30,33]. The problem is, that these methods did no show any success in patients with PD, because the beginning of therapy is to late, the number of surviving neurons is too small. Therefore, an early diagnosis may provide a better time point for the submission of therapeutic strategies who can protect against the cell death occurring and to prevent the progress of the disease.

The problem underlying the present invention is solved by the use of a diagnostic test, whereby the test comprises the gene expression patterns of one or more genes with or without their combination.

The inventors have found 54 gene candidates (Table 1) encoding for specific proteins, which shows an increase or a decrease of expression in PD comparing to control. Using these gene patterns as molecular markers, single or in combination, a specific and sensitive method is created for early detection of individuals, who will develop PD.

Comparing to the methods used today, this method has the advantage not to use rare genetically mutations or familial history of the disease, but rather use general gene expression changes which occur also in sporadic PD. These gene expression alterations may be caused not only as a consequence of specific genetically background, but also of environmental background. Therefore, this method will detect not only patients who have gene mutations, but also the sporadic patients very early in the development of the disease.

The invention will provide for the first time the possibility to have an early diagnostic way for PD before the symptoms appear.

The problem underlying the present invention is solved by the determination of gene expression pattern by extraction of RNA from biological material, preferably blood samples or biopsy samples of skin. The RNA will be isolated rapidly by a commercial available Kit. The RNA will be tested through hybridization to a customized GeneChip array containing the 54 selected genes and relevant house-keeping genes serving for normalization, or by means of Real-time-reverse-transcription-PCR for each of the 54 genes. The gene expression pattern will be determined via comparison to the expression of positive and negative control RNA (with de-novo PD and healthy subjects, respectively). The pattern of the gene expression received via one of the techniques should be similar to the pattern described in table 1 in order to define the subject as PD patient.

Polypeptides, proteins and derivatives coded by up to 54 genes, which are increased or decreased in PD patients compared to healthy subjects, will be used as markers in a test, performed in biological material, preferably in blood. This test method is easy and rapidly to do and relative inexpensive.

Table 1: Gene changes expected in PD

a) Inflammatory related genes

Chemokines C-X-C

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
1	209774_x_at	chemokine (C-X-C motif) ligand 2	Down	M57731.1	Produced by activated monocytes and neutrophils and expressed at sites of inflammation	Small cytokines (intecrine/chemokine), interleukin-8 like
2	206336_at	chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2)	Up	NM_002993.1	Cytokine, Chemotaxis, Heparin-binding, Signal	Small cytokines (intecrine/chemokine), interleukin-8 like
3	214146_s_at	pro-platelet basic protein (chemokine (C-X-C motif) ligand 7)	Up	R64130	Cytokine, Connective tissue, Growth factor, Chemotaxis, Mitogen, Platelet, Signal, 3D-structure	Small cytokines (intecrine/chemokine), interleukin-8 like
4	203915_at	chemokine (C-X-C motif) ligand 9	Up	NM_002416.1	Cytokine, Interferon induction, Inflammatory response, Signal	Small cytokines (intecrine/chemokine), interleukin-8 like
5	205242_at	chemokine (C-X-C motif) ligand 13 (B-cell chemoattractant)	Up	NM_006419.1	Cytokine, Chemotaxis, Signal, Inflammatory response	Small cytokines (intecrine/chemokine), interleukin-8 like

Chemokine C-C

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
6	220351_at	chemokine (C-C motif) receptor-like 1	Up	NM_016557.1	Receptor for SCYA2/MCP1, SCYA8/MCP2, SCYA13/MCP4. SCYA19/MIP3B/ELC, SCYA21/SLC and SCYA25/TECK.	7 transmembrane receptor (rhodopsin family)
7	216598_s_at	chemokine (C-C motif) ligand 2	Down	S69738.1	Chemotactic factor that attracts monocytes and basophils but not neutrophils or eosinophils. Augments monocyte anti-tumor activity. Has been implicated in the pathogenesis of diseases characterized by monocytic infiltartas, like psoriasis, rheumazoid arthritis or atherosclerosis. May be involved in the recruitment of monocytes into the arterial wall during the disease process of atherosclerosis. Binds to CCR2 and CCR4.	Small cytokines (intecrine/chemokine), interleukin-8 like
8	205392_s_at	chemokine (C-C motif) ligand 14	Up	NM_004166.1	Has weak activities on human monocytes and acts via receptors that also recognize MIP-1 alpha. It induced intracellular Ca(2+) changes and enzyme release, but no chemotaxis, at concentrations of 100-1,000 nM, and was inactive on lymphocytes, neutrophils, and eosinophils leukocytes. Enhances the proliferation of CD34 myeloid progenitor cells.	Small cytokines (intecrine/chemokine), interleukin-8 like 2
9	207354_at	chemokine (C-C motif) ligand 16	Up	NM_004590.1	SHOWS CHEMOTACTIC ACTIVITY FOR LYMPHOCYTES AND MONOCYTES BUT NOT NEUTROPHILS. ALSO SHOWS POTENT MYELOSUPPRESSIVE ACTIVITY, SUPPRESSES PROLIFERATION OF MYELOID PROGENITOR CELLS. RECOMBINANT SCYA16 SHOWS CHEMOTACTIC ACTIVITY FOR MONOCYTES AND THP-1 MONOCYTES, BUT NOT FOR RESTING LYMPHOCYTES AND NEUTROPHILS. INDUCES A CALCIUM FLUX IN THP-1 CELLS THAT WERE DESENSITIZED BY PRIOR EXPRESSION TO RANTES.	Small cytokines (intecrine/chemokine), interleukin-8 like
10	210549_s_at	chemokine (C-C motif) ligand 23	Up	U58913.1	SHOWS CHEMOTACTIC ACTIVITY FOR MONOCYTES, RESTING T-LYMPHOCYTES, AND NEUTROPHILS, BUT NOT FOR ACTIVATED LYMPHOCYTES. INHIBITS PROLIFERATION OF MYELOID PROGENITOR CELLS IN COLONY FORMATION ASSAYS. THIS PROTEIN CAN BIND HEPARIN. BINDS CCR1.	Small cytokines (intecrine/chemokine), interleukin-8 like
11	207955_at	chemokine (C-C motif) ligand 27	Up	NM_006664.1	CHEMOTACTIC FACTOR THAT ATTRACTS SKIN-ASSOCIATED MEMORY T-LYMPHOCYTES. MAY PLAY A ROLE IN MEDIATING HOMING OF LYMPHOCYTES TO CUTANEOUS SITES. BINDS TO CCR10.	

Chemokine C

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
12	221468_at	chemokine (C motif) receptor 1	Up	NM_005283.1		
13	206365_at	chemokine (C motif) ligand 1	Up	NM_002995.1	CHEMOTACTIC ACTIVITY FOR LYMPHOCYTES BUT NOT FOR MONOCYTES OR NEUTROPHILS.	Small cytokines (intecrine/chemokine), interleukin-8 like

Interleukins

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
14	207433_at	interleukin 10	Up	NM_000572.1	Inhibits the synthesis of a number of cytokines, including IFN-gamma, IL-2, IL-3, TNF and GM-CSF produced by activated macrophages and by helper T cells.	Interleukin 10
15	208200_at	interleukin 1, alpha	Up	NM_000575.1	PRODUCED BY ACTIVATED MACROPHAGES, IL-1 STIMULATES THYMOCYTE PROLIFERATION BY INDUCING IL-2 RELEASE, B-CELL MATURATION & PROLIFERATION, & FIBROBLAST GROWTH FACTOR ACTIVITY. IL-1 PROTEINS ARE INVOLVED IN THE INFLAMMATORY RESPONSE, BEING IDENTIFIED AS ENDOGENOUS PYROGENS, AND ARE REPORTED TO STIMULATE THE RELEASE OF PROSTAGLANDIN AND COLLAGENASE FROM SYNOVIAL CELLS.	Interleukin-1 / 18, Interleukin-1 propeptide
16	207539_s_at	interleukin 4	Up	NM_000589.1	IL-4 PARTICIPATES IN AT LEAST SEVERAL B-CELL ACTIVATION PROCESSES AS WELL AS OF OTHER CELL TYPES. IT IS A COSTIMULATOR OF DNA-SYNTHESIS. IT INDUCES THE EXPRESSION OF CLASS II MHC MOLECULES ON RESTING B-CELLS. IT ENHANCES BOTH SECRETION AND CELL SURFACE EXPRESSION OF IGE AND FC RECEPTOR FOR IGE (CD23) ON BOTH LYMPHOCYTES AND MONOCYTES.	Interleukin 4
17	206295_at	interleukin 18 (interferon-gamma-inducing factor)	Up	NM_001562.1	AUGMENTS NATURAL KILLER-CELL ACTIVITY IN SPLEEN CELLS AND STIMULATES INTERFERON GAMMA PRODUCTION IN T HELPER TYPE 1 CELLS.	Secreted.
18	207008_at	interleukin 8 receptor, beta	Up	NM_001557.1	RECEPTOR TO INTERLEUKIN-8, WHICH IS A POWERFUL NEUTROPHILS CHEMOTACTIC FACTOR. BINDING OF IL-8 TO THE RECEPTOR CAUSES ACTIVATION OF NEUTROPHILS. THIS RESPONSE IS MEDIATED VIA A G-PROTEIN THAT ACTIVATE A PHOSPHATIDYLINOSITOL-CALCIUM SECOND MESSENGER SYSTEM. THIS RECEPTOR BINDS TO IL-8 WITH A HIGH AFFINITY AND TO GRO/MGSA AND NAP-2 ALSO WITH A HIGH AFFINITY.	7 transmembrane receptor (rhodopsin family)
19	221271_at	interleukin 21	Up	NM_021803.1		
20	208344_x_at	interferon, alpha 13	Up	NM_006900.2		Death domain, TNFR/NGFR cysteine-rich region
21	214581_x_at	tumor necrosis factor receptor superfamily, member 21	Down	BE568134	May activate NF-kappa-B and JNK and promote apoptosis.	
22	206278_at	platelet-activating factor receptor	Up	D10202.1	RECEPTOR FOR PLATELET ACTIVATING FACTOR, A CHEMOTACTIC PHOSPHOLIPID MEDIATOR THAT POSSESSES POTENT INFLAMMATORY, SMOOTH- MUSCLE CONTRACTILE AND HYPOTENSIVE ACTIVITY. SEEM TO MEDIATE ITS ACTION VIA A G PROTEIN THAT ACTIVATE A PHOSPHATIDYLINOSITOL - CALCIUM SECOND MESSENGER SYSTEM.	7 transmembrane receptor (rhodopsin family)
23	208048_at	tachykinin receptor 1	Up	NM_015727.1	THIS IS A RECEPTOR FOR THE TACHYKININ NEUROPEPTIDE SUBSTANCE P. IT IS PROBABLY ASSOCIATED WITH G PROTEINS THAT ACTIVATE A PHOSPHATIDYLINOSITOL-CALCIUM SECOND MESSENGER SYSTEM.	7 transmembrane receptor (rhodopsin family)

b) Ubiquitin-proteasome system

Ubiquitination

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
24	207974_s_at	S-phase kinase-associated protein 1A (p19A)	Down	NM_003930.1	Essential component of the SCF (SKP1-CUL1-F-box protein) ubiquitin ligase complex, which mediates the ubiquitination of proteins involved in cell cycle progression, signal transduction and transcription. In the SCF complex, serves as an adapter that links the F-box protein to CUL1.	Skp1 family, dimerisation domain, Skp1 family, tetramerisation domain
25	206624_at	ubiquitin specific protease 9, Y chromosome (fat facets-like Drosophila)	Down	NM_004654.2	MAY FUNCTION AS A UBIQUITIN-PROTEIN OR POLYUBIQUITIN HYDROLASE INVOLVED BOTH IN THE PROCESSING OF UBIQUITIN PRECURSORS AND OF UBIQUITINATED PROTEINS. MAY THEREFORE PLAY AN IMPORTANT ROLE REGULATORY ROLE AT THE LEVEL OF PROTEIN TURNOVER BY PREVENTING DEGRADATION OF PROTEINS THROUGH THE REMOVAL OF CONJUGATED UBIQUITIN.	Ubiquitin carboxyl-terminal hydrolase
26	210338_s_at	heat shock 70kDa protein 8	Down	AB034951.1	Chaperone. Isoform 2 may function as an endogenous inhibitory regulator of HSC70 by competing the cochaperones.	Hsp70 protein
27	208608_s_at	syntrophin, beta 1 (dystrophin-associated protein A1, 59kDa, basic component 1)	Up	NM_021021.1	Adapter protein that binds to and probably organizes the subcellular localization of a variety of membrane proteins. May link various receptors to the actin cytoskeleton and the dystrophin glycoprotein complex.	PDZ domain (Also known as DHR or GLGF), PH domain

Vesicular and membrane traffic

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
28	214441_at	syntaxin 6	Up	NM_005819.1	Involved in intracellular vesicle trafficking.	SNARE domain
29	205924_at	RAB3B, member RAS oncogene family	Down	BC005035.1	Protein transport. Probably involved in vesicular traffic (By similarity).	Ras family
30	205461_at	RAB35, member RAS oncogene fan	Up	NM_006861.1	POSSESS GTPASE ACTIVITY, GTP-binding protein/GTPaseexperimental evidence Hydrolaseexperimental evidence	Ras family
31	208550_s_at	nucleoporin 155kDa	Down	NM_004298.1	ESSENTIAL COMPONENT OF NUCLEAR PORE COMPLEX. NUCLEOPORINS MAY BE INVOLVED BOTH IN BINDING AND TRANSLOCATING PROTEINS DURING NUCLEOCYTOPLASMIC TRANSPORT (BY SIMILARITY).	Non-repetitive/WGA-negative nucleoporin
32	205857_at	solute carrier family 18 (vesicular monoamine), member 2	Down	AI269290	INVOLVED IN THE ATP-DEPENDENT VESICULAR TRANSPORT OF BIOGENIC AMINE NEUROTRANSMITTERS. REQUISITE FOR VESICULAR AMINE STORAGE PRIOR TO SECRETION VIA EXOCYTOSIS.	(VMAT2)
33	205896_at	solute carrier family 22 (organic cation transporter), member 4	Down	NM_003059.1		
34	219561_at	coatomer protein complex, subunit zeta 2	Up	NM_016429.1	THE COATOMER IS A CYTOSOLIC PROTEIN COMPLEX THAT BINDS TO DILYSINE MOTIFS AND REVERSIBLY ASSOCIATES WITH GOLGI NON-CLATHRIN-COATED VESICLES, WHICH FURTHER MEDIATE BIOSYNTHETIC PROTEIN TRANSPORT FROM THE ER, VIA THE GOLGI UP TO THE TRANS GOLGI NETWORK. COATOMER COMPLEX IS REQUIRED FOR BUDDING FROM GOLGI MEMBRANES, AND IS ESSENTIAL FOR THE RETROGRADE GOLGI-TO-ER TRANSPORT OF DILYSINE-TAGGED PROTEINS. THE ZETA SUBUNIT MAY BE INVOLVED IN REGULATING THE COAT ASSEMBLY AND, HENCE, THE RATE OF BIOSYNTHETIC PROTEIN TRANSPORT DUE TO ITS ASSOCIATION-DISSOCIATION PROPERTIES WITH THE COATOMER COMPLEX (By similarity).	Clathrin adaptor complex small chain

c) Glutamate and dopamine metabolism

Glutamate and dopamine neurotransmission

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
35	210577_at	calcium-sensing receptor (hypocalciuric hypercalcemia 1, severe neonatal hyperparathyroidism)	Up	U20760.1	SENSE CHANGES IN THE EXTRACELLULAR CONCENTRATION OF CALCIUM IONS. THE ACTIVITY OF THIS RECEPTOR IS MEDIATED BY A G- PROTEIN THAT ACTIVATES A PHOSPHATIUYLINOSITOL-CALCIUM SECOND MESSENGER SYSTEM.	7 transmembrane receptor (metabotropic glutamate family), Receptor family ligand binding region
36	207454_at	glutamate receptor, ionotropic, kainate 3	Up	NM_000831.1	Receptor for glutamate. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system. The postsynaptic actions of Glu are mediated by a variety of receptors that are named according to their selective agonists. This receptor binds domoate > kainate >> L-glutamate = quisqualate >> AMPA = NMDA.	Receptor family ligand binding region, Ligand-gated ion channel
37	214559_at	dopamine receptor D3	Up	NM_000796.1	THIS IS ONE OF THE FIVE TYPES (D1 TO D5) OF RECEPTORS FOR DOPAMINE. THE ACTIVITY OF THIS RECEPTOR IS MEDIATED BY G PROTEINS WHICH INHIBIT ADENYLYL CYCLASE.	7 transmembrane receptor (rhodopsin family)
38	207732_s_at	discs, large (Drosophila) homolog 3 (neuroendocrine-dlg)	Up	NM_021120.1	INTERACTS WITH THE CYTOPLASMIC TAIL OF THE NMDA RECEPTOR SUBUNIT NR2B (BY SIMILARITY).	Guanylate kinase, PDZ domain (Also known as DHR, or GLGF)

d) Amyloidosis and glucose metabolism involved genes

Amyloidosis and glucose metabolism

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
39	210938_at	insulin promoter factor 1, homeodomain transcription factor	Up	U30329.1	ACTIVATES INSULIN, SOMATOSTATIN, GLUCOKINASE, ISLET AMYLOID POLYPEPTIDE AND GLUCOSE TRANSPORTER TYPE 2 GENE TRANSCRIPTION. PARTICULARLY INVOLVED IN GLUCOSE-DEPENDENT REGULATION OF INSULIN GENE TRANSCRIPTION. BINDS PREFERENTIALLY THE DNA MOTIF 5'-[CT]TAAT[TG]-3'. DURING DEVELOPMENT, SPECIFIES THE EARLY PANCREATIC EPITHELIUM, PERMITTING ITS PROLIFERATION, BRANCHING AND SUBSEQUENT DIFFERENTIATION. AT ADULT STAGE, REQUIRED FOR MAINTAINING THE HORMONE-PRODUCING PHENOTYPE OF THE BETA-CELL.	Homeobox domain
40	208510_s_at	peroxisome proliferative activated receptor, gamma	Up	NM_015869.1	Receptor that bind peroxisome proliferators such as hypolipidemic drugs and fatty acids. Once activated by a ligand, the receptor binds to a promoter element in the gene for acyl-CoA oxidase and activates its transcription. It therefore controls the peroxisomal beta-oxidation pathway of fatty acids. Key regulator of adipocyte differentiation and glucose homeostasis.	Nuclear.
41	220570_at	found in inflammatory zone 3	Up	NM_020415.2	Hormone that seems to suppress insulin ability to stimulate glucose uptake into adipose cells. Potentially links obesity to diabetes.	Secreted.
42	204261_s_at	presenilin 2 (Alzheimer disease 4)	Up	AA716657	MAY PLAY A ROLE IN INTRACELLULAR SIGNALING AND GENE EXPRESSION OR IN LINKING CHROMATIN TO THE NUCLEAR MEMBRANE. MAY FUNCTION IN THE CYTOPLASMIC PARTITIONING OF PROTEINS. IS INVOLVED IN THE PROTEOLYTICAL PROCESSING OF AMYLOID PRECURSOR PROTEIN (APP) AND OF NOTCH1.	Presenilin
43	209660_at	transthyretin (prealbumin, amyloidosis type I)	Up	AF162890.1	Thyroid hormone-binding protein. Probably transports thyroxine from the bloodstream to the brain.	Transthyretin precursor (formerly prealbumin)
44	210081_at	advanced glycosylation end product-specific receptor	Up	AB036432.1	Mediates interactions of advanced glycosylation end products (AGE). These are nonenzymatically glycosylated proteins which accumulate in vascular tissue in aging and at an accelerated rate in diabetes. Receptor for amyloid beta peptide.	Type I membrane protein (isoform 1); secreted (isoform 2)
45	203676_at	glucosamine (N-acetyl)-6-sulfatase (Sanfilippo disease IIID)	Up	NM_002076.1	Hydrolase, Glycoprotein, Lysosome, Signal, Mucopolysaccharidosis	Sulfatase

e)Signal transduction

Signal transduction

Number	Affy ID	GENE NAME	EXPECTED EXPRESSION IN BLOOD	GeneBank	Function	Protein Family
146	204579_at	fibroblast growth factor receptor 4	Up	NM_002011.2	RECEPTOR FOR ACIDIC FIBROBLAST GROWTH FACTOR. DOES NOT BIND TO BASIC FIBROBLAST GROWTH FACTOR. BINDS FGF19.	Immunoglobulin domain, Protein kinase domain
147	205014_at	heparin-binding growth factor binding protein	Up	NM_005130.1	Inhibitor or repressor not recorded	
148	203879_at	phosphoinositide-3-kinase, catalytic, delta polypeptide	Up	U86453.1	Transferase, Kinase, Multigene family	Phosphatidylinositol 3- and 4-kinase, C2 domain, PI3-kinase family, p85-binding domain, PI3-kinase family, ras-binding domain, Phosphoinositide 3-kinase family, accessory domain (PIK domain)
149	203878_at	phosphoinositide-3-kinase, catalytic, gamma polypeptide	Up	NM_002649.1	3-PHOSPHORYLATES THE CELLULAR PHOSPHONOSITIDE PTDINS-4,5-BIPHOSPHATE (PTDINS(4,5)P2).	Phosphatidylinositol 3- and 4-kinase, C2 domain, PI3-kinase family, ras-binding domain, Phosphoinositide 3-kinase family, accessory domain (PIK domain)
150	208370_at	growth differentiation factor 5 (cartilage-derived morphogenetic protein-1)	Up	NM_000557.2	COULD BE INVOLVED IN BONE FORMATION.	Transforming growth factor beta like domain, TGF-beta propeptide
151	208614_at	epidermal growth factor (beta-urogastrone)	Up	NM_001963.2	THE GROWTH FACTOR STIMULATES THE GROWTH OF VARIOUS EPIDERMAL AND EPITHELIAL TISSUES IN VIVO AND IN VITRO AND OF SOME FIBROBLASTS IN CELL CULTURE.	Low-density lipoprotein receptor repeat class B
152	206254_at	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	Up	NM_002502.1	P100 IS THE PRECURSOR OF THE P52 SUBUNIT OF THE NUCLEAR FACTOR NF-KAPPA-B, WHICH BINDS TO THE KAPPA-B CONSENSUS SEQUENCE 5'-GGRNNYYCC-3', LOCATED IN THE ENHANCER REGION OF GENES INVOLVED IN IMMUNE RESPONSE AND ACUTE PHASE REACTIONS. THE PRECURSOR PROTEIN ITSELF DOES NOT BIND TO DNA. ISOFORM P49 IS A SUBUNIT OF THE NF-KAPPA-B PROTEIN COMPLEX, WHICH STIMULATES THE HIV ENHANCER IN SYNERGY WITH P65.	Ankyrin repeat, Death domain, Rel homology domain (RHD), IPT/TIG domain
53	207535_s_at	nitric oxide synthase 2A (inducible, hepatocytes)	Up	L24553.1	PRODUCES NITRIC OXIDE (NO) WHICH IS A MESSENGER MOLECULE WITH DIVERSE FUNCTIONS THROUGHOUT THE BODY. IN MACROPHAGES, NO MEDIATES TUMORICIDAL AND BACTERICIDAL ACTIONS.	FAD binding domain, Flavodoxin, Oxidoreductase NAD-binding domain, Nitric oxide synthase, oxygenase domain
54	210037_s_at	v-fos FBJ murine osteosarcoma viral oncogene homolog	Down	BC004490.1	NUCLEAR PHOSPHOPROTEIN WHICH FORMS A TIGHT BUT NON-COVALENTLY LINKED COMPLEX WITH THE C-JUN/AP-1 TRANSCRIPTION FACTOR. C-FOS HAS A CRITICAL FUNCTION IN REGULATING THE DEVELOPMENT OF CELLS DESTINED TO FORM AND MAINTAIN THE SKELETON. IT IS THOUGHT TO HAVE AN IMPORTANT ROLE IN SIGNAL TRANSDUCTION, CELL PROLIFERATION AND DIFFERENTIATION.	Low-density lipoprotein receptor repeat class B

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Claims

1. Use of molecular markers for Parkinson's disease, whereby the markers comprise genes described in table 1 as chemokines (C-X-C motif) ligand 2; chemokines (C-X-C motif) ligand 6; chemokines (C-X-C motif) ligand 7, chemokines (C-X-C motif) ligand 9; chemokines (C-X-C motif) ligand 13, chemokine (C-C motif) receptor like 1; chemokine (C-C motif) ligand 2, chemokine (C-C motif) ligand 14; chemokine (C-C motif) ligand 16, chemokine (C-C motif) ligand 23; chemokine (C-C motif) ligand 27, chemokine (C motif) ligand 1; interleukin 10, interleukin alpha 1; interleukin 4, interleukin 18; interleukin beta 8 receptor, interleukin 21; interleukin alpha 13, interferon alpha 13; tumor necrosis factor receptor superfamily member 21; platelet-activating factor receptor; tachykinin receptor 1; S-phase kinase-associated protein 1A; ubiquitin specific protease 9 Y chromosome; heat shock 70 kDa protein 8; syntrophin beta 1; syntaxin 6; RAB3B; RAB35; nucleoporin 155 kDa; solute carrier family 18 member 2; solute carrier family 22 member 4; coatomer protein complex subunit zeta 2; calcium-sensing receptor; glutamate receptor; dopamine receptor D3; discs large (Drosophila) homolog 3; insulin promoter factor 1; peroxisome proliferative activated receptor gamma; gene named with the gene bank code: NM 020415.2; presenilin 2; transthyretin; gene named with the gene bank code: AB036432.1; glucosamine (N-acetyl)-6-sulfatase; fibroplast growth factor receptor 4, heparin-binding growth factor binding protein; phosphoinositide-3-kinase delta polypeptide; phosphoinositide-3-kinase gamma polypeptide; growth differentiation factor 5; epidermal growth factor; nuclear factor of kappa light polypeptide gene enhancer in B-cells 2; nitric oxide synthase 2A; v-fos FBJ murine osteosarcoma viral homolog.

2. Use of molecular markers for detection of Parkinson's disease, whereby the markers comprise polypeptides expressed by the genes in claim 1.

3. Use of molecular markers for detection of Parkinson's disease, whereby the markers comprise proteins and derivatives thereof expressed by the genes in claim 1.

4. A method for using molecular markers single or in combination (claim 1-3) to detect Parkinson disease.

5. A diagnosis test for Parkinson's disease comprising molecular markers (claim 1-3) single or in combination.

Diagnostic test for Parkinson's disease detection

Abstract

The present invention is related to a diagnosis test for Parkinson's disease detection at an early stage, whereby the test comprises as molecular markers

a) gene expression alterations of up to 54 genes

b) polypeptides and/or proteins expressed by one or more of the 54 genes.